1. SCIENTIFIC ABSTRACT

Adenocarcinoma of the prostate is the most common cancer diagnosis in American males, and the second leading cause of cancer death. One out of 11 men will develop clinically significant prostate cancer in his lifetime. During 2004, an estimated 230,100 men will be diagnosed with prostate cancer and 29,900 will die from prostate cancer in the United States.(1)

While the majority of patients are now diagnosed with clinically localized disease, 30-40% of patients will fail local therapy (radiation or surgery) within 10 years as evidenced by a rise in PSA.(2-4) For patients that have rising PSA following radical prostatectomy, the average time to development of metastatic disease is 8 years.(5) Androgen deprivation therapy is the cornerstone of initial treatment of metastatic disease, and recently docetaxel based regimens have been shown to prolong overall survival in patients with progressive disease on androgen deprivation therapy.(6;7)

Development of vaccines for prostate cancer thus represents a novel therapeutic approach. Over the past decade, serum PSA levels have been used as a biochemical marker for disease recurrence. For patients with metastatic androgen insensitive prostate cancer, newer treatment strategies, including cancer vaccines, are being designed in an attempt to slow or prevent the development of overt metastatic disease.

PSA is a potential target for a prostate cancer vaccine due to its restricted expression on prostate cancer and normal prostatic epithelium. Since PSA is a "self"-antigen, vaccines and vaccine strategies must be developed to enhance the immunogenicity of PSA. The proposed vaccine strategy represents a third-generation design that elicits a T-cell immune response to cells expressing PSA and has been shown to break tolerance to this self-antigen. Pre-clinical and clinical studies with a range of vaccines have demonstrated that the induction of T-cell responses directed against a self-antigen can lead to anti-tumor activity in the absence of toxicity.

CTLA-4 is an important regulator of T-cell homeostasis. It becomes expressed about 2-3 days after T-cells become activated and has a much higher affinity for B7.1 and B7.2 than their stimulatory ligand, CD28 does. Its binding to the B7 costimulatory molecules results in down regulation of the number of antigen specific T-cells. Thus when a human T cell encounters an antigen in vivo, there is stimulation and proliferation of antigen specific T-cells through the stimulatory B7.1/CD28 interaction. This acute response, often to a microbial infection, is then generally followed by resolution of the infection and down regulation of the number of antigen specific T-cells through the inhibitory CTLA-4/B7.1 interaction. Therefore, by preventing interactions between CTLA-4 and its ligands by using a neutralizing or blocking antibody, it is possible to sustain and potentiate immune responses against weak antigens.

Preclinical studies have shown that anti-CTLA-4 antibodies augment the anti-tumor effect of vaccines. In addition, MDX-010 (human anti-CTLA-4 mAb) has demonstrated preliminary evidence of activity in several disease states including prostate cancer. The activity may be significantly more enhanced in combination with an active vaccine strategy as seen in our preclinical studies and as seems to be indicated by studies in patients with melanoma.

This study utilizes a dose escalation Phase I design followed by a single arm phase II portion. In the Phase I portion, patients in all cohorts receive initial priming with rV- PSA(L155)/TRICOM and GM-CSF s.c. followed by boosting with rF- PSA(L155)/TRICOM with anti-CTLA-4 initiated with the first boosting vaccine. The anti-CTLA-4 will be given for a maximum of 6 monthly cycles. The toxicities seen during 28 days after the second anti-CTLA-4 will be used for dose escalation. The phase II portion of the trial will look at the combination of vaccine and anti-CTLA-4 (at the MTD dose) to further characterize clinical response, safety, and immunological effect.

Important objectives of this trial include evaluation of safety, clinical responses, PSA kinetics and immunologic effects of this vaccine strategy in combination with anti-CTLA-4. The objective responses will be analyzed by RECIST criteria and the immunological effects will be assessed with ELISPOT assay of peripheral blood before and after vaccination.

The maximum accrual to the trial is 50. We estimate that we will accrue approximately 1-2 patients a month in the phase I portion and 2-4 patients a month in the phase II portion leading to full accrual within 2- 3 years.